Abdominal Radiology (2019) 44:3463–3479
https://doi.org/10.1007/s00261-019-02128-7

INTERVENTIONAL RADIOLOGY

Correlation between SACE (Subjective Angiographic Chemoembolization Endpoint) score and tumor response and its impact on survival after DEB-TACE in patients with hepatocellular carcinoma

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Published online: 23 July 2019

Abstract

Purpose To asses angiographic and computed tomographic success criteria during and after transcatheter arterial drug-eluting bead chemoembolization (DEB-TACE) in patients with hepatocellular carcinoma (HCC) and its impact on progression-free survival (PFS) and overall survival (OS).

Methods In this retrospective single-center study, 50 patients with unresectable HCC having undergone DEB-TACE from January 2010 to July 2015 were assessed. The angiographic endpoint was classified by Subjective Angiographic Chemoembolization Endpoint (SACE) scale. Relative tumor density in arterial (D_{Art}) and portal venous phase (D_{PV}) computed tomography post- versus pre-DEB-TACE were calculated, respectively. Tumor response according to modified Response Criteria in Solid Tumors (mRECIST) was assessed. Univariate Kaplan–Meier and Cox regression analysis were carried out.

Results SACE scores I, II, III, and IV were found in 1 (2%), 20 (40%), 15 (30%), and 14 (28%) patients, respectively. Median OS and PFS were 14.2 and 5.5 months, respectively. Death rates at 6 months, 1 year and 2 years were 24%, 38%, and 52%, respectively. SACE score during DEB-TACE significantly correlated with local and overall mRECIST results (local: $p < 0.001$, $r = 0.49$, overall: $p = 0.042$, $r = 0.29$) and inversely correlated with D_{PV} ($p = 0.005$, $r = -0.40$). In univariate analysis, progressive disease (PD) according to mRECIST and increase of D_{Art} and D_{PV} were associated with significantly shorter PFS. Modified RECIST independently predicted OS (hazard ratio for complete remission vs. PD = 0.15, 95% confidence interval 0.03–0.68, $p = 0.014$).

Conclusions A direct impact of SACE on PFS or OS could not be shown. However, SACE significantly correlated with local and overall mRECIST tumor response that again significantly predicted OS. We therefore postulate an indirect impact of SACE on OS. Consequently, complete embolization should be attempted.

Keywords Hepatocellular carcinoma · Transcatheter arterial drug-eluting bead chemoembolization · TACE · Subjective Angiographic Chemoembolization Endpoint scale · SACE · Tumor density · mRECIST

Introduction

Every year, roughly 780000 people die from liver cancer worldwide [1]. The hepatocellular carcinoma (HCC) represents > 90% of liver cancers next to cholangiocellular carcinoma (< 10%) [2]. Nowadays, it's the sixth most often malignant tumor. There were 841000 cases of liver cancer in 2018 recorded worldwide, which constitutes 4.7% of all cancer entities. The incidence in men is more than twice as high as in women [1].

According to the Barcelona Clinic Liver Cancer (BCLC)-classification, transcatheter arterial chemoembolization (TACE) is the recommended treatment for unresectable intermediate stage HCC [3, 4] and the only non-curative treatment prolonging survival next to chemotherapy [5]. Furthermore, TACE can be used for downstaging prior to surgery or transplantation. Drug-eluting bead transarterial chemoembolization (DEB-TACE) evolved from the earlier

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common conventional TACE (cTACE). Instead of placing a chemotherapeutic agent followed by embolic material in the tumor nourishing artery during cTACE, embolic particles loaded with chemotherapeutic agents are administered during DEB-TACE inducing tumor necrosis and local tumor toxicity with less systemic side effects [6, 7]. The one-year survival rate of patients with HCC after DEB-TACE ranges from 45 to 94% with Child–Pugh stage, portal invasion and single tumor burden being prognostic factors for survival [8–12].

Further factors predicting progression-free (PFS) and overall survival (OS) after TACE in patients with HCC have been investigated. The most commonly used factor is the radiological imaging evaluation of tumor response assessed in multi-detector computed tomography (MDCT) or magnetic resonance imaging (MRI) [13, 14]. Common response criteria for HCC are the modified Response Criteria in Solid Tumors (mRECIST) and the European Association for the Study of the Liver (EASL) criteria. It has been shown that complete remission (mRECIST) and tumor response (EASL) are significant predictors for OS [15, 16]. Tumor density in CT has been analyzed as response criterion. Kwan et al. correlated radiological parameters with necrosis of > 90% according to histopathological examination in patients with HCC undergoing cTACE with three chemotherapeutic agents, ethiodized oil followed by gelatin sponge embolizing material. A high tumor density (HU) in post-TACE CT (pre-contrast phase) due to high accumulation of ethiodized oil within the tumor nodule was correlated significantly with developing > 90% necrosis in histopathological analysis (OR 1.2, $p = 0.005$) [17]. As during DEB-TACE agents with less density are used and tumor necrosis is expected, a reduction of density in the tumor is expected. The Choi criteria were established to assess tumor response taking into account tumor attenuation (Hounsfield Units) as well as change of tumor diameter. Initially, they were used to evaluate gastrointestinal stromal tumors after imatinib treatment [18]. Choi et al. measured tumor densities in monophasic and triphasic CTs. Having used the time-bolus technique, the values of tumor densities were normalized to those of muscles and arteries. As they found no significant difference between use of the absolute tumor density and the normalized density, they used the absolute tumor density for further calculations [18]. Beuzit et al. compared RECIST to Choi criteria in patients with cholangiocellular carcinoma after selective internal radiation therapy and found the Choi criteria to outstand RECIST criteria in predicting OS [19]. Imai et al. stated that an increase in lesion density 1 week after TACE versus immediately after was an independent predictor for lower local recurrence rate of HCC (hazard ratio (HR) 0.18, $p = 0.002$) [20]. Density measurements (HU) of HCC in arterial phase of CT represent quantitative tumor enhancement [21].

There is a lack of studies evaluating density change after DEB-TACE as a response criterion and its impact on survival and tumor progress.

Furthermore, chemoembolization endpoints and their impact on survival have been addressed [22]. Lewandowski et al. established the Subjective Angiographic Chemoembolization Endpoint (SACE) classification scheme uniting change of antegrade arterial flow in the tumor feeding artery and change of tumor blush in the angiograms post- versus pre-TACE [23]. Another chemoembolization endpoint was investigated by de Korompay et al. finding that the change of parenchymal blood volume in HCC during chemoembolization predicts tumor response in patients with unresectable HCC [24].

The aim of the current study was to investigate the SACE score, density change in the tumor after DEB-TACE and mRECIST criteria in patients with unresectable HCC. The hypothesis was that a high SACE score correlated with density reduction in HCC after DEB-TACE and leads to high tumor response and therefore to longer PFS and OS.

Methods

Patients

In a retrospective single-center clinical survey from January 2010 to July 2015, 65 patients with inoperable HCC underwent DEB-TACE with Epirubicin or Doxorubicin. The diagnosis process of HCC was based on the guidelines of the American Association for the Study of Liver Diseases (AASLD) [25]. The recommendation for DEB-TACE therapy was given by an interdisciplinary liver tumor board and made on an individual basis. Patients were excluded in case of lack of a baseline CT before and a control CT after one to six DEB-TACEs. One of the patients died due to renal failure (UICC IVa, Child–Pugh A) during the hospital stay. As a result, 50 patients were included in the study. Baseline characteristics are shown in Table 1.

Chemoembolization procedure

During DEB-TACE, DC Beads (Device Technologies, Belrose, Australia) loaded with Epirubicin or Doxorubicin and of sizes from 30 to 100 µm, 100 to 300 µm, 300 to 500 µm, or 500 to 700 µm were placed into the tumor feeding artery and the dose was chosen to reach complete devascularization of the target lesions and ranged from 7 to 75 mg. If a complete hemostasis could not be reached, in selected cases Lipiodol or 150–250 µm non-pheric PVA particles (Contour, Terumo Corporation, Tokyo, Japan) were additionally injected (Lipiodol in 40 of 158 and PVA in 1 of 158

Table 1 Baseline patient characteristics, $n = 50$

Parameter	All patients ($n = 50$)	SACE I + II ($n = 21$)	SACE III ($n = 15$)	SACE IV ($n = 14$)	p
Male gender	43 (86%)	18 (86%)	13 (87%)	12 (86%)	0.996
Age (years)	71.5 (33–82)	71 (33–81)	72 (46–82)	72 (51–80)	0.97
Tumor size of target lesions (cm)	7 (2–18.6)	9.6 (2.2–18.6)	5.3 (2.3–16.8)	3.7 (2–12.3)	0.001
Number of tumors					0.327
1	22 (44%)	10 (48%)	8 (53%)	4 (29%)	
2–5	15 (30%)	4 (19%)	4 (27%)	7 (50%)	
> 5	13 (26%)	7 (33%)	3 (20%)	3 (21%)	
Child–Pugh classification					0.344
0	10 (20%)	4 (19%)	5 (33%)	1 (7%)	
A	30 (60%)	12 (57%)	7 (47%)	11 (79%)	
B	8 (16%)	3 (14%)	3 (20%)	2 (14%)	
C	2 (4%)	2 (10%)	0 (0%)	0 (0%)	
Cause of cirrhosis					0.347
Hepatitis B	1 (2%)	0 (0%)	1 (7%)	0 (0%)	
Hepatitis C	8 (16%)	3 (14%)	3 (20%)	2 (14%)	
Ethyl toxic	10 (20%)	5 (24%)	2 (13%)	3 (21%)	
Autoimmune/PSC	2 (4%)	0 (0%)	0 (0%)	2 (14%)	
Unknown	19 (38%)	10 (48%)	4 (27%)	5 (36%)	
Portal hypertension	16 (32%)	5 (24%)	3 (20%)	8 (57%)	0.058
Proof of Ascites	9 (18%)	1 (5%)	4 (27%)	4 (29%)	0.116
UICC stages					0.159
I	4 (8%)	0 (0%)	3 (20%)	1 (7%)	
II	13 (26%)	4 (19%)	6 (40%)	3 (21%)	
III	17 (34%)	10 (48%)	2 (13%)	5 (36%)	
IV	16 (32%)	7 (33%)	4 (27%)		
Additional therapy after DEB-TACE	16 (32%)	9 (56%)	3 (19%)	4 (25%)	0.332
Transplantation[a]	2 (4%)				
Radiofrequency ablation[a]	4 (6%)				
Atypical liver resection[a]	4 (8%)				
ALPPS[a]	1 (2%)				
Chemotherapy	4 (8%)				
Radiation	2 (4%)				
PVE	4 (8%)				

The sum of additional therapies is higher than the patient number stated as some patients received more than one additional therapy. To calculate differences, the Pearson χ^2 (asymp. significance) was used for ordinal or nominal data and the Kruskal–Wallis test for continuous data. Values are number of patients with percentage in parentheses. For continuous data values are median and range in parentheses. Percentages may not add up to 100 owing to rounding

PSC primary sclerosing cholangitis, *UICC* Union internationale contre le cancer, *ALPPS* Associating Liver Partition and Portal Vein Ligation for Staged Hepatectomy, *PVE* portal vein embolization, *Nota bene* as one RFA has been done in the other liver lobe than the target lesion for DEB-TACE, this single patient has not been censored

[a]Censored in survival analysis ($n = 10$)

DEB-TACE sessions). DEB-TACE was repeated up to 10 times in intervals of 4 to 8 weeks.

Subjective Angiographic Chemoembolization Endpoint scale (SACE)

Before, during, and after DEB-TACE, digital subtraction angiography series were acquired. The changes in tumor blush and in flow in the tumor feeding artery after the DEB-TACE intervention were classified according to SACE scale, which was established by Lewandowski et al. [23]. Antegrade blood flow reaching the target tumor after chemoembolization was compared to the arteriograms just before DEB-TACE. The blood flow proximal to the tumor was classified as unchanged, reduced, or disrupted. Accordingly, the residual tumor blush visible on the post- versus

pre-DEB-TACE angiograms was compared. The tumor blush was classified as unchanged, reduced, or completely eliminated. Table 2 shows the four stages of the SACE score which resulted from the two classifications. Figure 1 displays angiograms before and after DEB-TACE with a SACE score IV indicating eliminated tumor blush and blood flow in the tumor feeding artery. In case of multiple tumors, the target tumor was analyzed. In case of repeated DEB-TACEs, the most effective (highest score) out of the first four sessions was entered in the analysis.

Radiological imaging

CT with a MDCT (Brilliance 40, Philips Medical Systems, The Netherlands) at a 40 × 1.25 mm collimation was performed at a maximum of 9 weeks before the first and after one to four, in one case after six, DEB-TACEs. The institutional standard time for control imaging was 2 to 4 weeks after the third DEB-TACE. The time differed in case of side effects, signs of progress or bridging before surgery as the reason for DEB-TACE. A first-year resident in visceral surgery controlled by an experienced attending radiologist (8 years of radiological education) evaluated the radiological imaging. Information about liver cirrhosis, portal hypertension, and the TNM-tumor stage was obtained.

Table 2 Subjective Angiographic Chemoembolization Endpoint scale (SACE) [23]

SACE score	Residual antegrade arterial flow	Residual tumor blush
I	Normal	Normal/reduced
II	Reduced	Reduced
III	Reduced	None
IV	None	None

Response assessment

The local and overall responses were assessed by modified Response Evaluation Criteria In Solid Tumors (mRECIST) [26]. Patients with response criteria stable disease (SD), partial remission (PR) or complete remission (CR) after one to four DEB-TACEs were classified as responders, those with progressive disease (PD) as non-responders. Subsequent surveillance imaging was generated every 2 to 7 months.

To assess another success criterion of the tumor to DEB-TACE, CT density measurements using the region-of-interest (ROI) circle on the target tumor and on the aorta were made. Hounsfield Units of the portal venous (PV) and arterial (Art) phase were noted. As the time-bolus technique (for contrast medium application) was used, to eliminate small time shifting between two CTs, tumor density was normalized to aorta density. Normalized tumor density in the baseline (T1) and the control CT (T2) were calculated, respectively [density $(D)_{PV,T1}/D_{Aorta,T1}$, $D_{Art,T1}/D_{Aorta,T1}$, $D_{PV,T2}/D_{Aorta,T2}$, $D_{Art,T2}/D_{Aorta,T2}$]. The relative density quotient at control point in comparison with the baseline was calculated for both phases. D_{PV} was used for results measured in PV phase and was calculated as $D_{PV,T2}/D_{Aorta,T2}$/

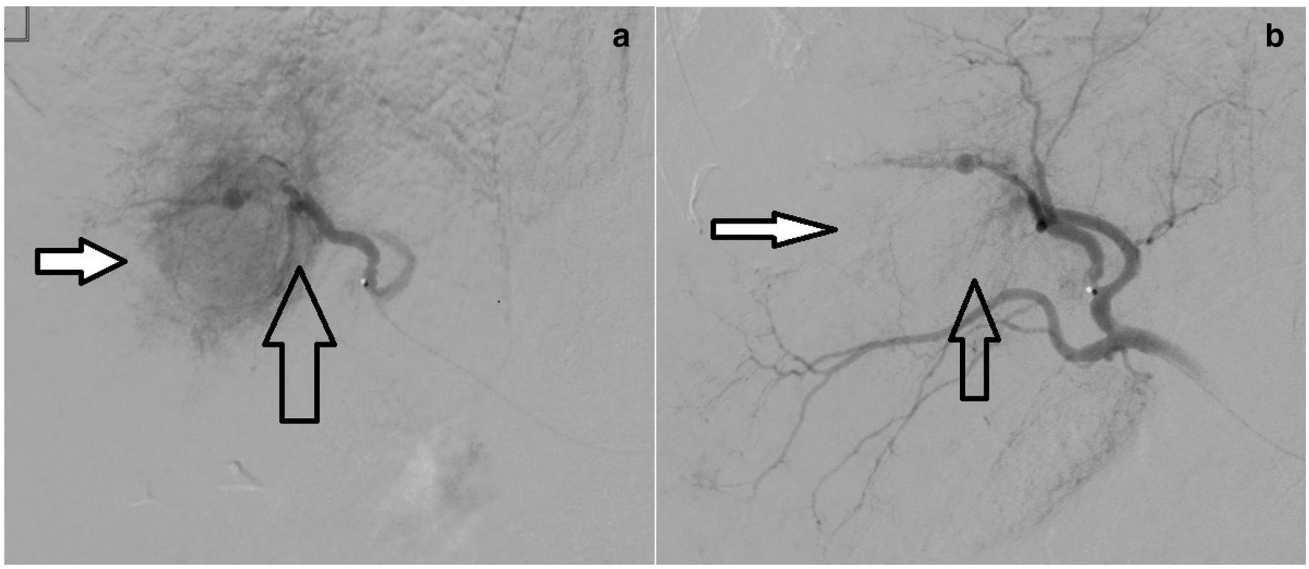

Fig. 1 **a** (Left) digital subtraction angiogram of a 71-year-old man with hepatocellular carcinoma (HCC) prior to transcatheter arterial drug-eluting bead chemoembolization (DEB-TACE) showing the tumor blush of the HCC (white colored arrow) and the tumor feeding artery (unfilled black arrow). **b** (Right) complete elimination of tumor blush (white colored arrow) and blood flow in the tumor feeding artery (unfilled black arrow) to Subjective Angiographic Chemoembolization Endpoint (SACE) level IV

$D_{PV,T1}/D_{Aorta,T1}$. D_{Art} was used for results measured in arterial phase scans and calculated as $D_{Art,T2}/D_{Aorta,T2}/D_{Art,T1}/D_{Aorta,T1}$. Two examples are shown in Figs. 2 and 3.

Statistical analysis

All patients were followed until either death or last follow-up. The time to tumor progression was defined as time from first DEB-TACE to control CT showing progress (according to mRECIST) or death and OS as time from first DEB-TACE (in Cox regression analysis as time from control CT) to death, censoring or last follow-up. The reasons of censoring were liver transplantation, radiofrequency ablation, or liver resection. As there were censored patients, a death rate instead of a survival rate was calculated.

SPSS version 22.0 (SPSS, Inc., Chicago, IL, USA) was used for the statistical analysis. Metric normal and not normal distributed data were expressed as mean ± standard deviation and median and range, respectively. Categorical data was expressed as absolute and relative frequency. Correlation between not normal distributed, continuous and categorical data or two categorical variables were calculated using the Spearman-ρ test.

The cumulative probability of OS and PFS were calculated by the univariate Kaplan–Meier method. The Log-rank test (Mantel–Cox test) was used to show differences between two groups concerning late survival. Analyzing variables in being predictive factors for OS, the Cox regression model was used. Results were expressed as HR with a 95% confidence interval (CI) and the associated p value. Significance for all tests was set at a p value less than 0.05.

Results

Periinterventional results

Fifty patients (43 men) with inoperable HCC underwent in total 158 DEB-TACEs. The date of the last follow-up evaluation was April 2017. Most patients underwent three DEB-TACE sessions (1–10). Epirubicin was the agent used most often. During DEB-TACE, in 89.8% the right or both branches of the hepatic artery were targeted. Mean length of hospital stay was 3.3 ± 2.7 days. Details are shown in Table 3.

Results of imaging response criteria

According to the angiograms, SACE stages I and II were found in 1 (2%) and 20 (40%) patients, respectively. Stage I occurring once, and stage II were aggregated in further calculations. Stages III and IV occurred in 15 (30%) and 14 (28%) patients, respectively.

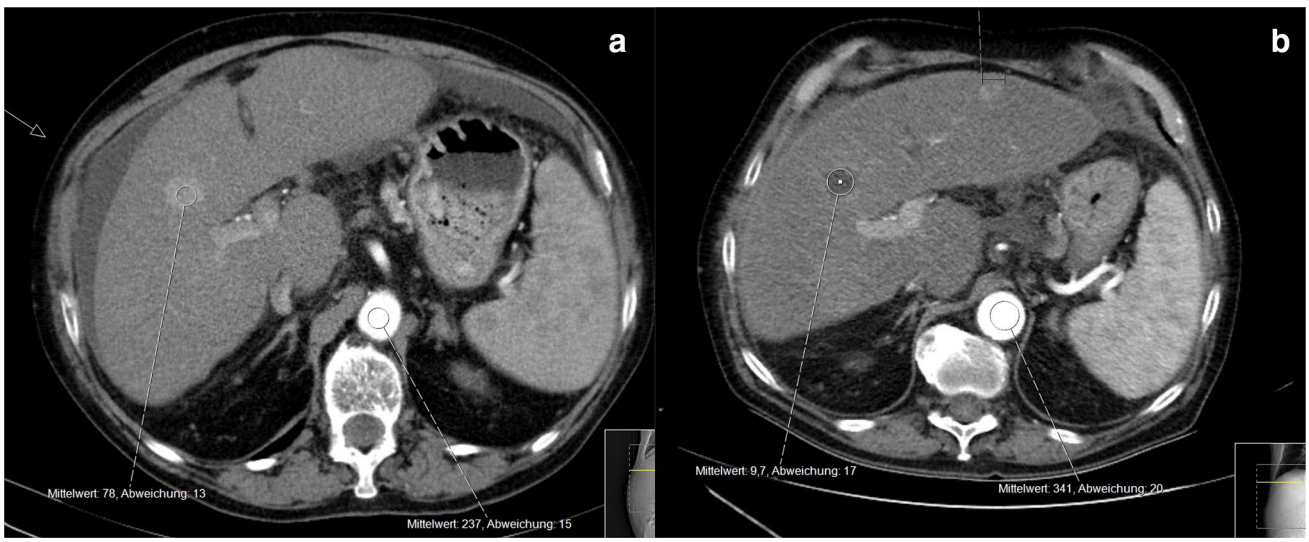

Fig. 2 **a** (Left) density measurements in mean of Hounsfield Units (HUs) in arterial phase CT pre-transcatheter arterial drug-eluting bead chemoembolization (DEB-TACE) in a 71-year-old patient with hepatocellular carcinoma. One measurement in the target tumor lesion (mean density 78 HU) and one in the aorta (mean density 237 HU). Tumor density normalized to aorta density at baseline (T1) was calculated by building a quotient: $D_{Art,T1}/D_{Aorta,T1} = 78/237$ HU. **b** (Right) the same measurements were taken on post-DEB-TACE CT (T2): mean tumor density 10 HU and mean aorta density 341 HU. Quotient of normalized tumor density: $D_{Art,T2}/D_{Aorta,T2} = 10/341$ HU. The grade of density change after DEB-TACE compared to baseline CT was then calculated by building a quotient of the post- and pre-DEB-TACE values of normalized density, respectively. Relative normalized density in HU 10/341/78/237 = 0.089 indicating a density drop of 91.1%

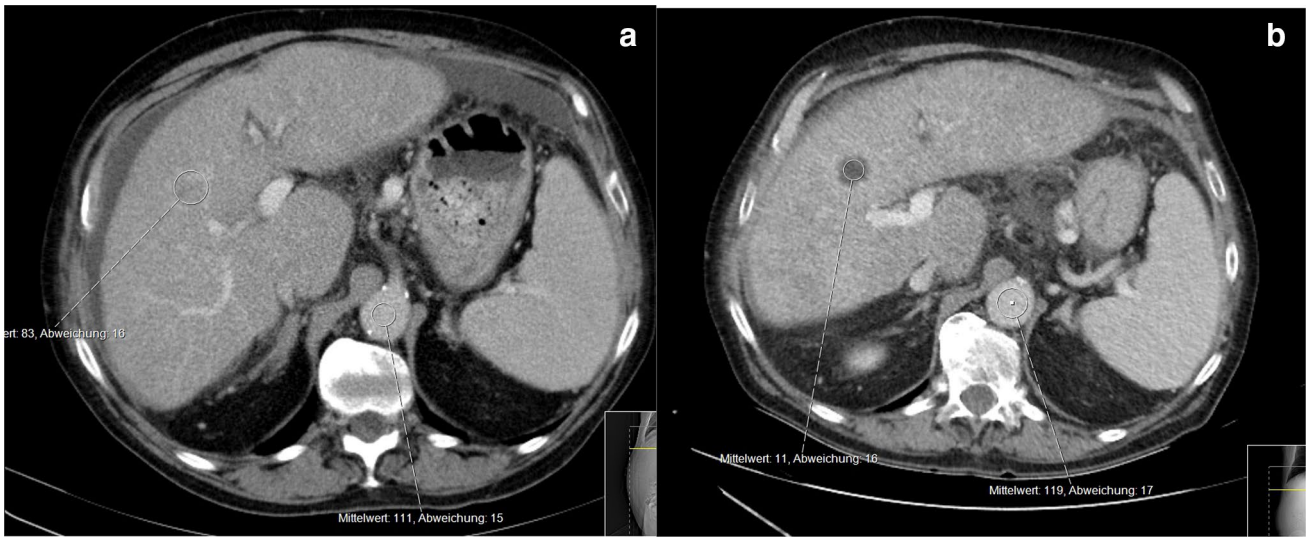

Fig. 3 **a** (Left) density measurements in mean of Hounsfield Units (HUs) in PV phase CT pre-transcatheter arterial drug-eluting bead chemoembolization (DEB-TACE) in a 71-year old patient with hepatocellular carcinoma. One measurement in the target tumor lesion (mean density 83 HU) and one in the aorta (mean density 111 HU). Tumor density normalized to aorta density at baseline (T1) was calculated by building a quotient of normalized tumor density: $D_{PV,T1}/D_{Aorta,T1} = 83/111$ HU. **b** (Right) the same measurements were taken on post-DEB-TACE CT (T2): mean tumor density 11 HU and mean aorta density 119 HU. Quotient of normalized tumor density: $D_{PV,T2}/D_{Aorta,T2} = 11/119$ HU. The grade of density change after DEB-TACE compared to baseline CT was then calculated by building a quotient of the post- and pre-DEB-TACE values of normalized density, respectively. Relative normalized density in HU $11/119/83/111 = 0.124$ indicating a density drop of 87.6%

Median D_{PV} was 0.83, which states a density decrease of 17%. Minimum D_{PV} was 0.04 (96% decrease) and maximum D_{PV} was 2.30 (increase of 130%). Mean D_{Art} was 0.70 ± 0.36 (Min: 0.00, Max: 1.87).

The assessment of the local tumor response according to mRECIST showed CR, PR, SD, and PD in 7 (14%), 14 (28%), 20 (40%), and 9 (18%) patients, respectively. Overall tumor response as CR, PR, SD, and PD was seen in 6 (12%), 11 (22%), 15 (30%), and 18 (36%) patients, respectively. There were 32 (64%) responders and 18 (36%) non-responders to DEB-TACE. Detailed imaging results are shown in Table 3.

Correlation analysis

SACE significantly correlated with local mRECIST tumor response ($p < 0.001$). The higher the SACE score and therefore the tumor blush and flow extinction, the higher the grade of response (correlation coefficient: $r = 0.49$). Correlation between SACE and overall mRECIST results was less but still significant ($p = 0.042$, $r = 0.29$). A significant difference in relative density (PV phase, D_{PV}) between the different SACE levels was found ($p = 0.015$). The pairwise comparison showed a significant difference between SACE I + II and IV ($p = 0.013$). SACE score and D_{PV} significantly correlated ($p = 0.005$, $r = -0.40$): the higher the SACE level, the lower the median relative density at control time (SACE I + II: 0.93, SACE III: 0.83, SACE IV: 0.65). Density change in the arterial phase scans, as well as density data of baseline CTs did not correlate with SACE score. Details are shown in Table 4.

Univariate analysis of overall and progression free survival after DEB-TACE

30 (60%) Patients died during the follow-up period, 10 (20%) patients were censored due to liver resection, transplantation, or radiofrequency ablation and 10 (20%) patients survived without being censored. Median OS of all patients was 14.1 (95% CI 7.2–21.0) months. The death rates at 6 months, 1 year, and 2 years were 24%, 38%, and 52%, respectively.

At the end of the study, 9 patients (18%) were progress free or censored. Median PFS of all patients was 5.5 (95% CI 4.3–6.8) months. In Kaplan–Meier analysis, the median PFS of SACE I + II, III, and IV were 3.8 (95% CI 1.3–6.4), 6.0 (95% CI 4.4–7.7), and 6.2 (95% CI 4.9–7.5) months, respectively ($p = 0.83$).

D_{PV} and D_{Art} results were classified in two categories according to decrease ($D < 1$) or increase ($D > 1$) of the normalized tumor density after DEB-TACE. Decrease of D_{PV} ($n = 34$) was associated with a significant PFS benefit over increase of D_{PV} ($n = 15$) [8.0 (95% CI 5.4–10.6) vs. 2.9 (95% CI 1.7–4.0) months, $p < 0.001$].

Table 3 Periinterventional and imaging results after DEB-TACE in patients with hepatocellular carcinoma

Parameter	Median (min–max)/*n* (%)
Number of sessions	158
Sessions per patient ($n=50$)	
Median	3 (1–10)
1	10 (20)
2	13 (26)
3	15 (30)
4–10	12 (24)
Agent ($n=158$)	
Epirubicin	151 (96)
Doxorubicin	7 (4)
Targeted liver artery ($n=158$)	
Right hepatic artery	86 (54.4)
Left hepatic artery	13 (8.2)
Both	59 (37.3)
Length of hospital stay (days)	3.3 ± 2.7
SACE score ($n=50$)	
Stage I	1 (2)
Stage II	20 (40)
Stage III	15 (30)
Stage IV	14 (28)
Normalized density in baseline CT, PV ($n=49$)	0.63 (0.23–7.09)
Normalized density in baseline CT, arterial ($n=47$)	0.27 (0.09–5.08)
Relative density: D_{PV} ($n=49$)	0.83 (0.04–2.30)
Relative density: D_{Art} ($n=45$)	0.70 ± 0.36
mRECIST: local response, $n=50$	
CR	7 (14)
PR	14 (28)
SD	20 (40)
PD	9 (18)
mRECIST: overall response, $n=50$	
CR	6 (12)
PR	11 (22)
SD	15 (30)
PD	18 (36)

SACE Subjective Angiographic Chemoembolization Endpoint scale, *mRECIST* modified Response Evaluation Criteria In Solid Tumors, *CR* complete remission, *PR* partial remission, *SD* stable disease, *PD* progressive disease

Decrease of D_{Art} ($n=36$) showed a PFS benefit over increase of D_{Art} ($n=9$) and had a median PFS of 6.7 (95% CI 3.3–10.1) versus 3.0 (95% CI 0.7–5.3) months, respectively ($p=0.026$). The median time to progression of the responders was 9.2 and of the non-responders 2.6 months (mRECIST), respectively ($p<0.001$).

Figures 4, 5, 6, and 7 show the cumulative probability of PFS for all patients ($n=50$) stratified by mRECIST tumor response, relative density after DEB-TACE (D_{PV}/D_{Art}), and SACE score.

There was no difference in OS rate by SACE level ($p=0.55$). Patients classified as SACE scores I + II had a median OS of 6.7 (95% CI 3.9–22.2) months, SACE score III of 14.2 (95% CI 10.3–84.3) and SACE score IV of 8.8 (95% CI 0–19.4) months.

The decrease ($n=34$) and increase ($n=15$) groups of D_{PV} had a median OS of 15.7 (95% CI 3.9–27.5) and 9.1 (95% CI 2.9–15.2, $p=0.17$) months. Patients with an increase ($n=9$) in D_{Art} didn't survive significantly shorter than patients with decrease ($n=36$) [6.7 (95% CI 0.2–13.3) vs. 14.2 (95% CI 2.1–26.3) months, $p=0.11$]. Overall responders to DEB-TACE lived significantly longer than non-responders (mRECIST: 37.0 vs. 5.5 months, $p<0.001$). Figures 8, 9, 10, 11, and 12 show the cumulative probability of OS for all patients stratified by local and overall mRECIST response status, relative density after DEB-TACE (D_{PV}/D_{Art}), and SACE score.

Table 4 Correlation between Subjective Angiographic Chemoembolization Endpoint scale (SACE) and tumor density data as well as mRECIST results after transcatheter arterial drug-eluting bead chemoembolization

	SACE	
	p	*r*
Density in baseline CT, PV, $n=49$	0.25	0.17
Density in baseline CT, arterial, $n=47$	0.39	− 0.13
Relative density: D_{PV}, $n=49$	**0.005**	**− 0.40**
Relative density: D_{Art}, $n=45$	0.15	− 0.22
Local mRECIST, $n=50$	**< 0.001**	**0.49**
Overall mRECIST, $n=50$	**0.042**	**0.29**

For analyzing correlation between SACE and mRECIST results or density data the Spearman-ρ correlation test was used. Significant results were shown in bold letters. Effect strength: according to Cohen (1992): $r=0.10$–0.29: weak effect, $r=0.30$–0.49: moderate effect, $r>0.49$: strong effect [35]

PV portal venous phase scans, *arterial* arterial phase scans, *mRECIST* modified Response Evaluation Criteria In Solid Tumors, *p* significance, *r* correlation coefficient

Cox regression analysis

Results of univariate Cox regression calculation are shown in Table 5. SD, PR, and CR (in both overall and local mRECIST assessment), target tumor size, and UICC stage were significant predictors for OS. Continuous variables of density changes (D_{PV}, D_{Art}) were used in Cox regression models. D_{PV} showed a trend to significance for predicting OS ($p=0.065$). Patients with an increase of D_{PV} had a 2.3-fold higher risk of dying during the study period than patients with a decrease after DEB-TACE (95% CI 0.96–5.88). Results of SACE were not significant.

Multivariate analysis of OS

In stepwise adjustments of multivariate Cox regression analysis, SACE confounded mRECIST and D_{PV} in predicting OS independent of UICC stage. When adding SACE in the multivariate Cox regression model, the *p* value for D_{PV} dropped to a significant level (0.035) and the HR rose by more than 10% (2.11 to 2.76). Local and overall mRECIST were significant independent predictors for OS (Table 6).

Discussion

The present single-center clinical study evaluated angiographic and CT graphic DEB-TACE success parameters in patients with inoperable HCC and its impact on PFS and OS. SACE level significantly correlated with local and overall mRECIST results ($p<0.001$ and 0.042) as well as with relative tumor density in PV phase CT after

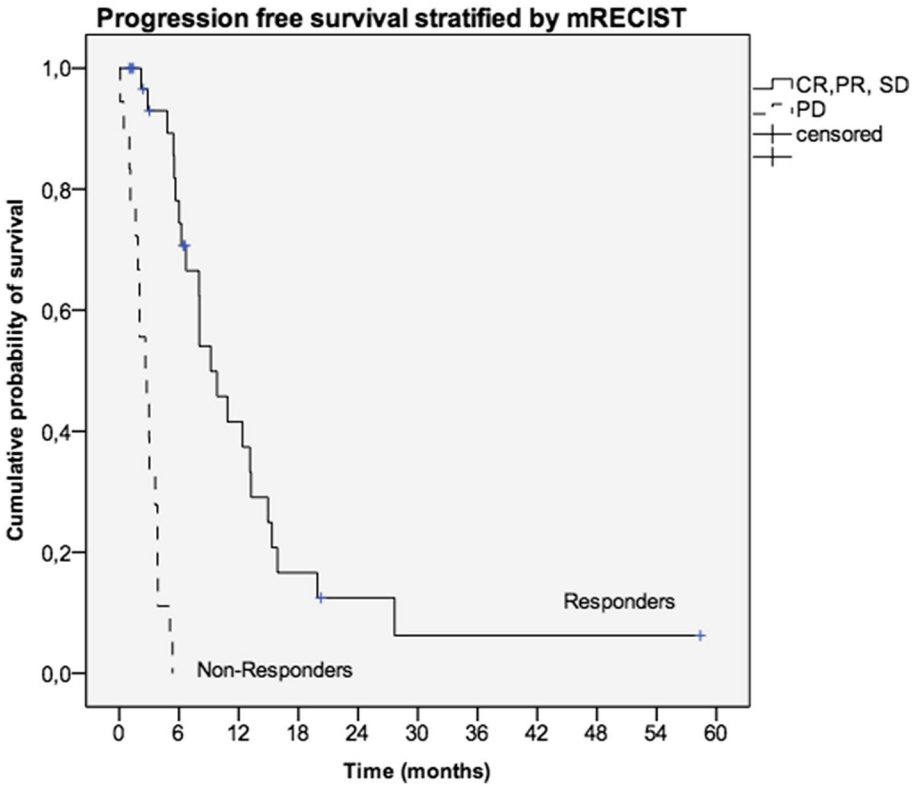

Fig. 4 Progression-free survival after DEB-TACE stratified by overall mRECIST ($n=50$). Responders (SD, PR, CR, $n=32$) and non-responders (PD, $n=18$) had a PFS of 9.2 (95% CI 6.5–11.9) and 2.6 (95% CI 1.1–4.1) months. Log-rank test: $p<0.001$. *mRECIST* modified Response Evaluation Criteria in Solid Tumors, *DEB-TACE* transarterial drug-eluting bead chemoembolization, *PD* progressive disease, *SD* stable disease, *PR* partial remission, *CR* complete remission, *CI* confidence interval, *PFS* progression free survival

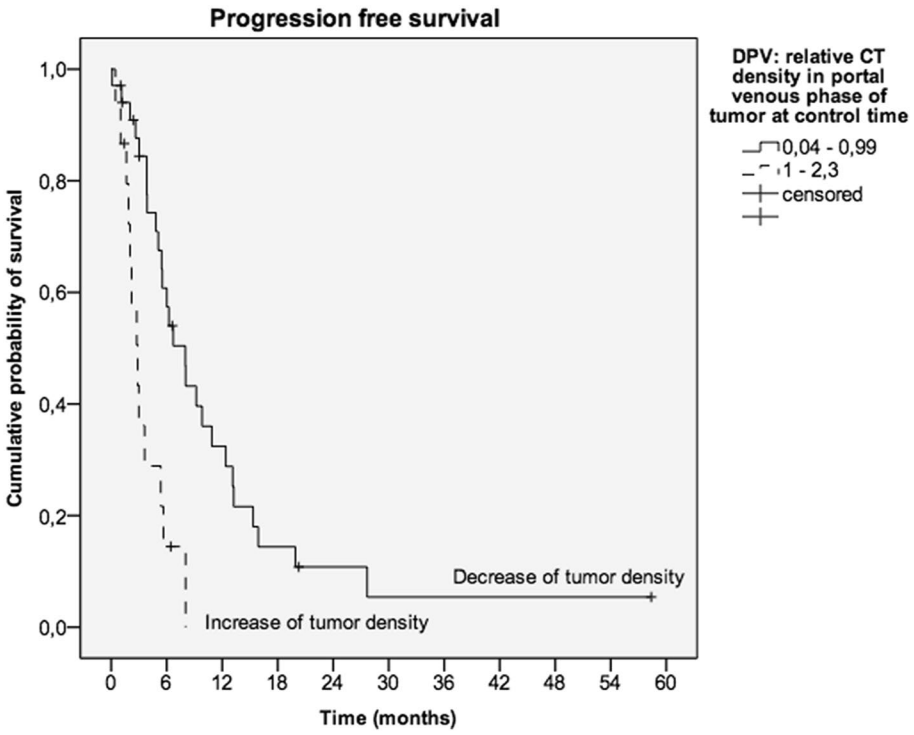

Fig. 5 Progression-free survival in patients with hepatocellular carcinoma—different density changes in the tumor [measured in portal venous phase scans (D_{PV})]. Decrease of D_{PV} ($D_{PV} < 1$, $n = 34$) was associated with a significant progression-free survival benefit over increase ($D_{PV} > 1$, $n = 15$) [8.0 (95% CI 5.4–10.6) vs. 2.9 (95% CI 1.7–4.0) months, log rank test: $p < 0.001$]

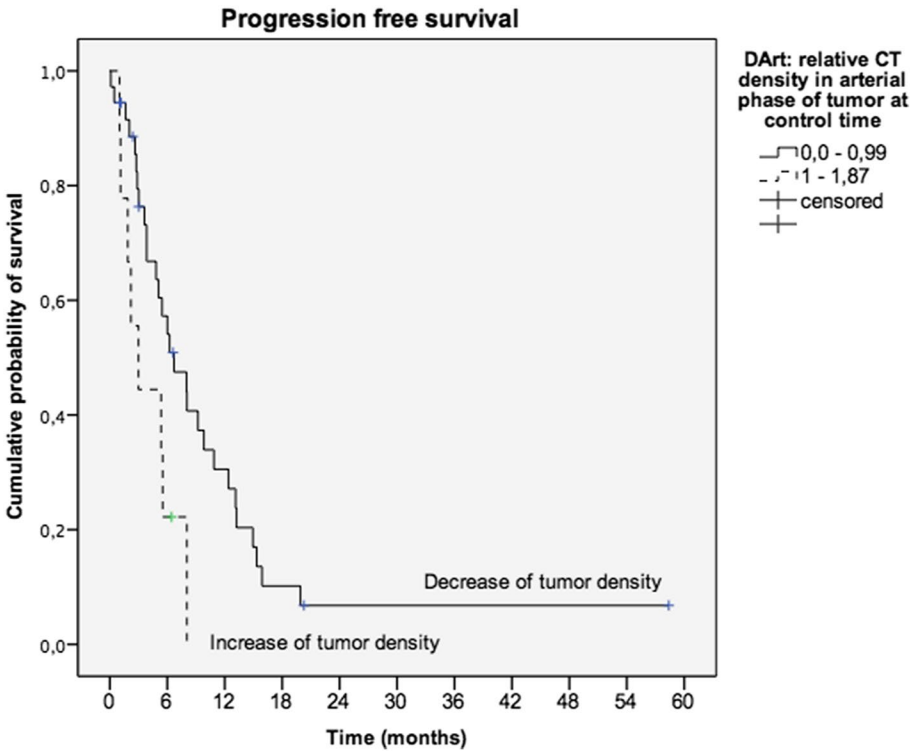

Fig. 6 Progression-free survival (PFS) in patients with hepatocellular carcinoma—different density changes in the tumor [measured in arterial phase scans (D_{Art})]. Decrease ($D_{Art} < 1$, $n = 36$) showed a PFS benefit over increase of D_{Art} ($D_{Art} > 1$, $n = 9$) and had a median PFS of 6.7 (95% CI 3.3–10.1) versus 3.0 (95% CI 0.7–5.3) months, log rank test: $p = 0.026$

versus before DEB-TACE (D_{PV}, $p = 0.005$). The median PFS and OS were 5.5 and 14.1 months with a death rate at one year of 38%. Tumor response to DEB-TACE (overall mRECIST), as well as decrease of density in arterial or PV phase scans after DEB-TACE (D_{PV} and $D_{Art} < 1$) were associated with a significant PFS benefit (mRECIST: $p < 0.001$, D_{PV}: $p < 0.001$, D_{Art}: $p = 0.026$). Independent predictors for OS were local mRECIST (HR 3.40, 95% CI 1.41–8.20, $p = 0.007$) and overall mRECIST (HR 5.15, 95% CI 2.21–12.04, $p < 0.001$). D_{PV} alone did not significantly

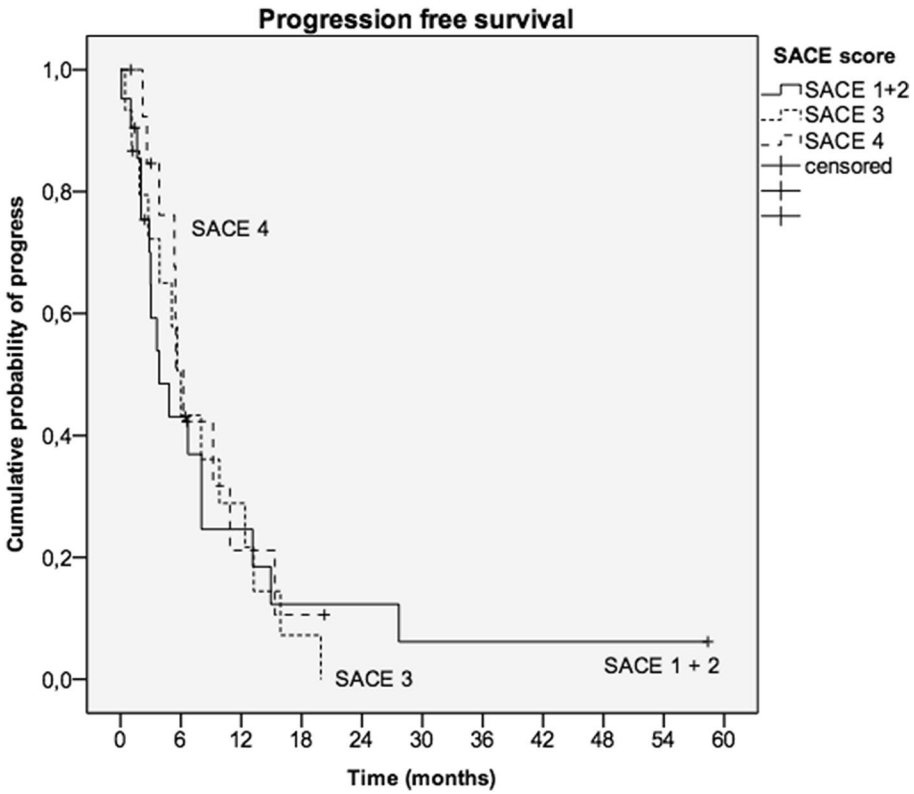

Fig. 7 Progression-free survival (PFS) in patients with hepatocellular carcinoma—Subjective Angiographic Chemoembolization Endpoint levels. The median PFS of all patients was 5.5 (95% CI 4.3–6.8). The median PFS of SACE I + II ($n = 21$), III ($n = 15$) and IV ($n = 14$) were 3.8 (95% CI 1.3–6.4), 6.0 (95% CI 4.4–7.7) and 6.2 (95% CI 4.9–7.5) months, respectively (log rank test: $p = 0.83$)

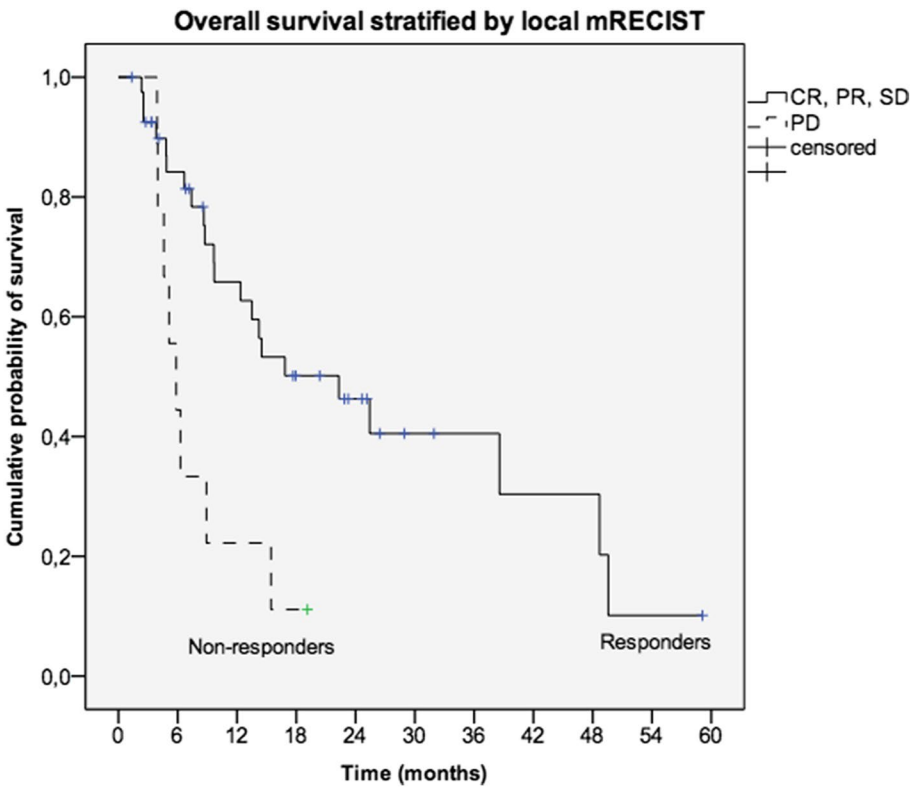

Fig. 8 Overall survival after DEB-TACE of the responders ($n = 41$) versus the non-responders ($n = 9$) (local mRECIST criteria). Median OS of Responders (local mRECIST CR, PR, SD) was 22.3 (95% CI 10.1–34.5) months and of non-responders (local mRECIST PD) 5.8 (95% CI 3.7–8.0) months. OS of all patients was 14.2 (95% CI 7.2–21.2) months. Log-rank test: $p = 0.005$. *mRECIST* modified Response Evaluation Criteria in Solid Tumors, *DEB-TACE* transarterial drug-eluting bead chemoembolization, *PD* progressive disease, *SD* stable disease, *PR* partial remission, *CR* complete remission

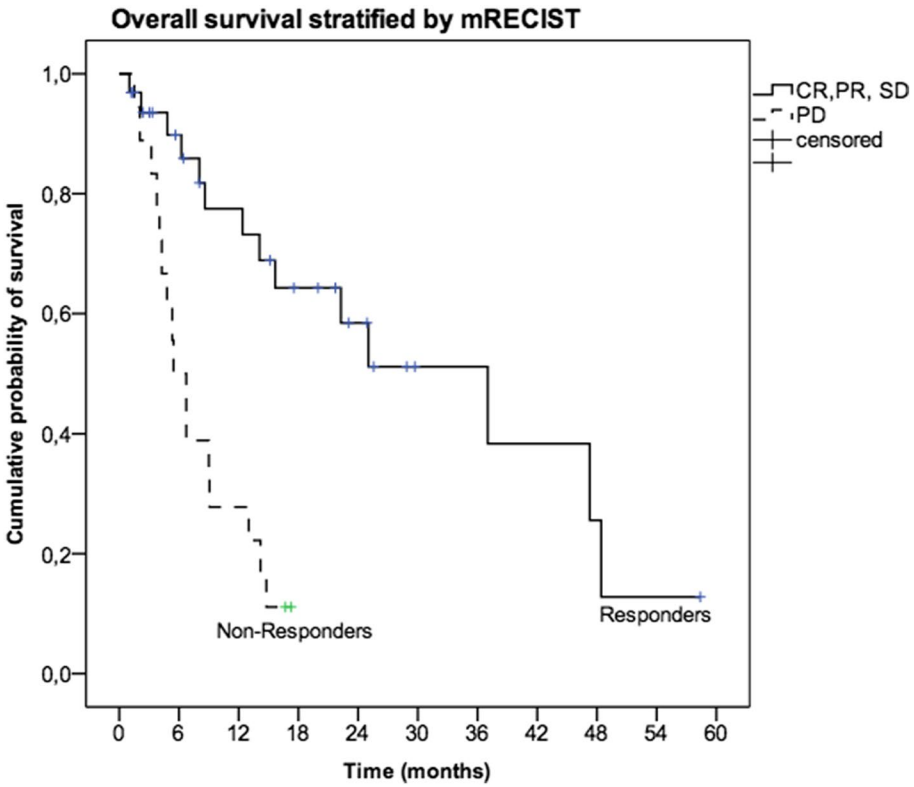

Fig. 9 Overall survival after DEB-TACE of the responders ($n=32$) versus the non-responders ($n=18$) (overall mRECIST criteria). Responders (SD, PR, CR) and non-responders (PD) had an overall survival of 37.0 (95% CI 16.9–57.2) and 5.5 (95% CI 3.5–7.4) months. Log-rank test: $p<0.001$. *mRECIST* modified Response Evaluation Criteria in Solid Tumors, *DEB-TACE* transarterial drug-eluting bead chemoembolization, *PD* progressive disease, *SD* stable disease, *PR* partial remission, *CR* complete remission

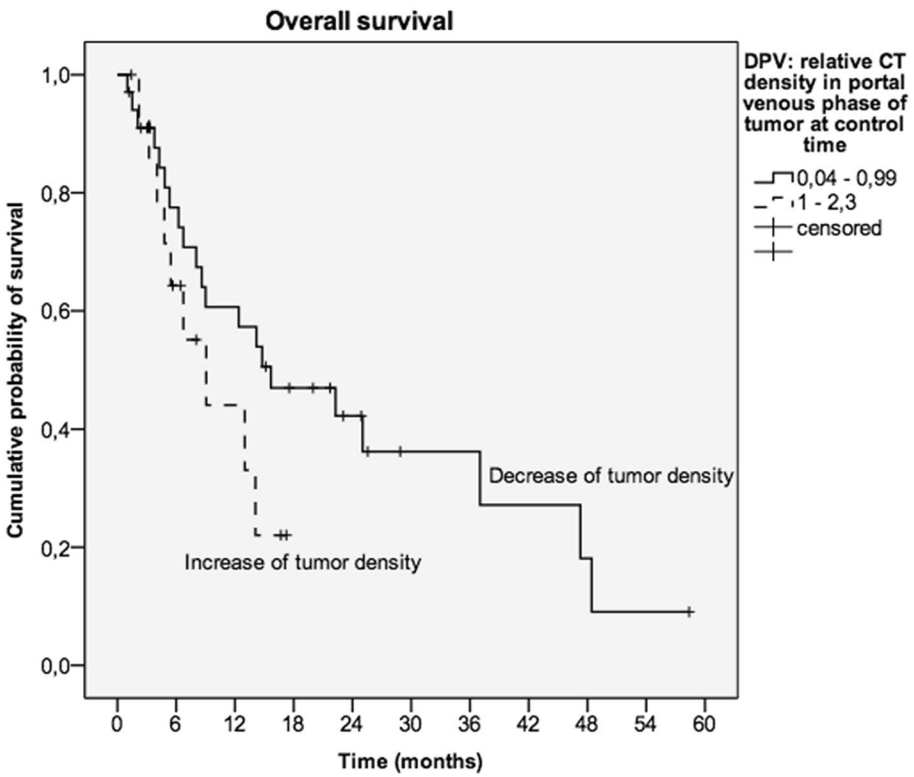

Fig. 10 Overall survival after transarterial drug-eluting bead chemoembolization in patients with hepatocellular carcinoma—different density changes in the tumor [measured in portal venous phase scans (D_{PV})]. The decrease ($n=34$) and increase ($n=15$) groups of D_{PV} had a median OS of 15.7 (95% CI 3.9–27.5) and 9.1 (95% CI 2.9–15.2) months. There was no significant difference in survival between decrease and increase of D_{PV} (log rank test: $p=0.17$)

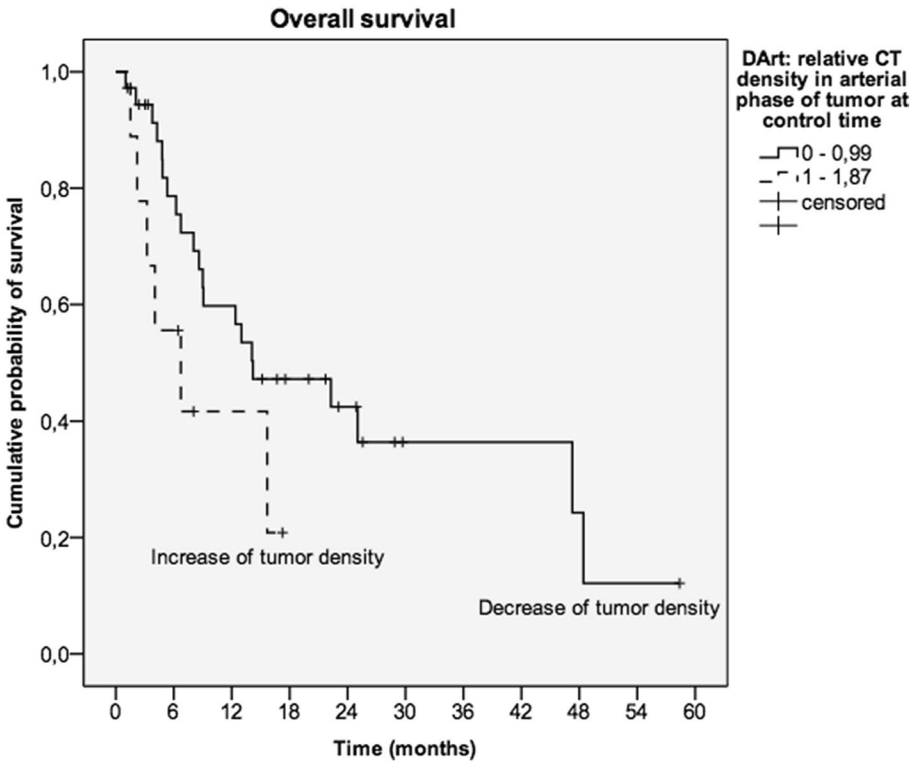

Fig. 11 Overall survival after transarterial drug-eluting bead chemoembolization in patients with hepatocellular carcinoma—different density changes in the tumor [measured in arterial phase scans (D_{Art})]. Patients with an increase ($n=9$) in D_{Art} had an OS of 6.7 (95% CI 0.2–13.3) versus 14.2 (95% CI 2.1–26.3) months in patients with a decrease ($n=36$) (log rank test: $p=0.11$)

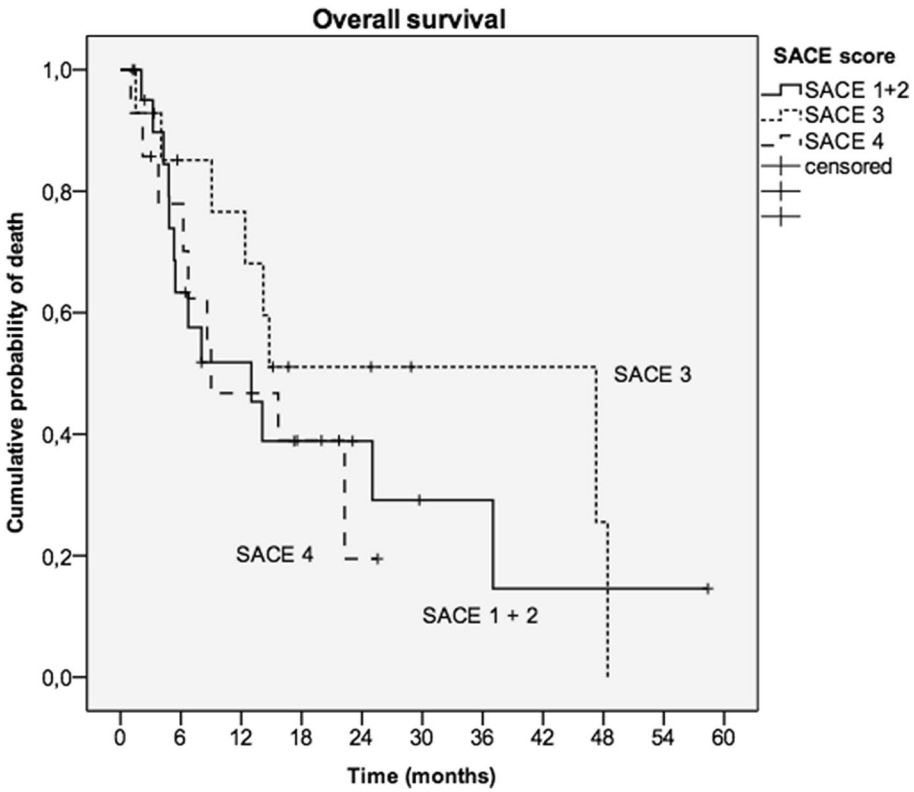

Fig. 12 Overall survival after transarterial drug-eluting bead chemoembolization in patients with hepatocellular carcinoma—Subjective Angiographic Chemoembolization Endpoint (SACE) levels during DEB-TACE (log rank test: $p=0.55$). Patients classified as SACE scores I + II ($n=21$) had a median OS of 6.7 (95% CI 3.9–22.2) months, SACE score III ($n=15$) of 14.2 (95% CI 10.3–84.3) and SACE IV ($n=14$) of 8.8 (95% CI 0–19.4) months

Table 5 Predictors for survival after transarterial drug-eluting bead chemoembolization in patients with hepatocellular carcinoma, results of univariate Cox regression analysis, $n = 50$

Model	Parameter	HR	95% CI	*p*
1	Age (per additional year)	0.97	0.94–1.0	0.08
2	Male versus female	1.97	0.59–6.60	0.27
3	Target tumor size (per cm)	1.1	1.0–1.21	**0.032**
4	Number of tumors			
	1	1 (Ref)		0.24
	2–5	1.60	0.64–4.0	0.32
	>5	2.10	0.89–4.96	0.09
5	UICC			
	Stages I–IIIa	1 (Ref)		
	Stages IIIb–IVb	2.97	1.34–6.56	**0.007**
6	Child–Pugh			
	0	1 (Ref)		0.54
	A	1.98	0.66–5.93	0.23
	B	2.56	0.71–9.19	0.15
	C	–	–	–
7	Density of target tumor in HU at baseline, PV ($n=49$)	0.50	0.11–2.40	0.39
8	Density of target tumor in HU at baseline, arterial ($n=47$)	1.29	0.8–2.0	0.27
9	D_{PV}: relative density after treatment ($n=49$) (PV)	2.34	0.95–5.79	0.065
10	D_{Art}: relative density after treatment ($n=45$) (arterial)	1.23	0.36–4.21	0.74
11	SACE			
	Stages I + II	1 (Ref)		0.56
	Stage III	0.67	0.28–1.62	0.37
	Stage IV	1.11	0.47–2.65	0.81
12	Local mRECIST			
	PD	1 (Ref)		
	SD	0.38	0.15–0.99	**0.047**
	PR	0.25	0.09–0.71	**0.010**
	CR	0.23	0.06–0.91	**0.036**
13	Overall mRECIST			
	PD	1 (Ref)		
	SD	0.21	0.08–0.61	**0.004**
	PR	0.19	0.06–0.59	**0.004**
	CR	0.15	0.03–0.68	**0.014**

For clarification, significant figures were shown in bold type

HR hazard ratio, *vs* versus, *UICC* Union internationale contre le cancer, *CT* computed tomography, *HU* Hounsfield Units, *SACE* Subjective Angiographic Chemoembolization Endpoint scale, *DEB-TACE* drug-eluting bead transcatheter arterial chemoembolization, *PV* portal venous phase CT, *arterial* arterial phase CT, *mRECIST* modified Response Evaluation Criteria in Solid Tumors

predict OS rate (HR = 2.34, 95% CI 0.95–5.79, $p = 0.065$). When taking SACE into the calculation, it showed to be a confounder of D_{PV} and mRECIST independently predicting OS (HR for D_{PV} 2.76, 95% CI 1.07–7.11, $p = 0.035$; HR for overall mRECIST 6.44, 95% CI 2.61–15.90, $p < 0.001$). D_{Art} and SACE score were not found independent predictors for OS.

As the decision for DEB-TACE was made individually in a tumor board, despite the AASLD guidelines recommending TACE for BCLC-B stage HCC, we included 16 patients (32%) showing organic metastases or lymphatic invasion of their HCC classified as UICC stage IV (BCLC-C). Two patients (4%) with Child–Pugh C cirrhosis (BCLC-D) were entered in the study. Kloeckner et al. and Wiggermann et al. entered 44.7% and 13.6% of patients with BCLC-C HCC in their study rather representing our patient sample [11, 27]. More unfavorable baseline characteristics of our patients were a higher percentage of Child–Pugh B/C cirrhosis (10% vs. 7% in the study of Song et al. [28]). These unfavorable baseline characteristics could be accountable for shorter OS and PFS rates.

One of our hypothesis was, that density decrease in the HCC lesion after DEB-TACE would be associated with tumor necrosis and could therefore be a significant response

Table 6 Predictors for survival after transarterial drug-eluting bead chemoembolization in patients with hepatocellular carcinoma, results of multivariate Cox regression analysis, stepwise adjustments, $n = 50$

Model	Parameter	HR	95% CI	p of density (D_{PV})
1.0	D_{PV}: relative density after treatment ($n=49$) (PV)	2.34	0.95–5.79	0.065
1.1	(1.0) + UICC	2.11	0.89–5.0	0.089
1.2	(1.1) + SACE	2.76	1.07–7.11	0.035
Model	Parameter	HR	95% CI	p of local mRECIST
2.0	Local mRECIST (PD vs. non-PD)	3.32	1.40–7.86	0.006
2.1	(2.0) + UICC	3.40	1.41–8.20	0.007
2.2	(2.1) + SACE	4.42	1.57–12.46	0.005
Model	Parameter	HR	95% CI	p of overall mRECIST
3.0	Overall mRECIST (PD vs. non-PD)	5.20	2.25–12.0	< 0.001
3.1	(3.0) + UICC	5.15	2.21–12.04	< 0.001
3.2	(3.1) + SACE	6.44	2.61–15.90	< 0.001

HR hazard ratio, *vs* versus, *UICC* Union internationale contre le cancer, *CT* computed tomography, *HU* Hounsfield Units, *SACE* Subjective Angiographic Chemoembolization Endpoint scale, *DEB-TACE* drug-eluting bead transcatheter arterial chemoembolization, *PV* portal venous phase CT, *mRECIST* modified Response Evaluation Criteria in Solid Tumors

and survival criterion. Choi et al. evaluated response criteria of gastrointestinal tumor after imatinib therapy taking into account not only tumor diameter, but also density change, reflecting areas of tumors with reduced vascularization. Measurements were taken in PV phase scans [18]. As the time-bolus technique during CT was used, the values of tumor densities were normalized to those of muscles and arteries. As they found no significant difference between use of the absolute tumor density and the normalized density, they used the absolute tumor density for further calculations [18]. To rule out any influence of the time-bolus technique, tumor density values normalized to the aorta were used in the present study. Ronot et al. found a survival benefit of Choi responders to sorafenib in HCC versus Choi non-responders [29]. In the present study, patients with a decrease of normalized tumor density measured in PV phase scans post- versus pre-DEB-TACE ($D_{PV} < 1$) had a significantly longer PFS (8.0 vs. 2.9 months, log rank test: $p < 0.001$) supporting the prior statement. The impact on OS in univariate Cox regression was not significant ($p = 0.065$, HR = 2.37, 95% CI = 0.96–5.86).

Rising D_{PV} negatively predicted OS at a significant level when adjusted for SACE and UICC stage ($p = 0.035$, HR = 2.76, 95% CI 1.07–7.11). This result has to be confirmed in preferably prospective studies with higher patient number.

Density measurements (HU) of HCC in arterial phase of CT represent quantitative tumor enhancement [21]. Kwan et al. analyzed post-TACE CT tumor enhancement after cTACE. Subjective absence of residual contrast enhancement correlated with histopathological near-complete necrosis (> 90%) [17]. Those findings strengthen our hypothesis that a computed tomographic density drop in HCC after DEB-TACE might be associated with higher tumor necrosis and therefore can be expected as tumor response criterion influencing survival. In the present study, a decrease of normalized tumor density (HU) in arterial phase CT after versus before DEB-TACE ($D_{Art} < 1$) was associated with a PFS benefit over density increase ($D_{Art} > 1$) (6.7 vs. 3.0 months, $p = 0.026$).

Whether arterial or PV phase is the preferable CT phase for density measurement as response criterion is still to be clarified. Discrepancies of univariate and multivariate analysis of OS might be due to a small patient number.

DEB-TACE is an established treatment for HCC. However, there is a variation of protocol details such as choice of chemotherapeutic agent, embolic material and particle size or end of embolization. Moreover, the endpoint of embolization is a very subjective affair. Next to the SACE, quantitative measurements of tumor perfusion or tumor blood volume post- versus pre-TACE have been used [24, 30, 31]. Jin et al. compared quantitative four-dimensional transcatheter intraarterial perfusion MRI (4D-TRIP-MRI) with the SACE scale and found a good correlation ($p < 0.001$) suggesting that SACE scale can be used to categorize patients according to embolic endpoints of TACE [31]. For the interventionist, the question is, whether stasis or substasis during TACE is the more favorable embolic endpoint to achieve the best

outcome for the patient. Gaba showed in a survey with 1157 participants of interventional radiologists of the Society of Interventional Radiology that 56% of the interventionists preferred substasis and 43% complete stasis as embolic endpoint [32]. Furthermore, study results suggested that substasis had a better effect on response and survival than overembolization or underembolization. This might be because of possible damage of healthy liver tissue due to ischemia [33, 34]. Jin et al. showed a significant survival benefit of HCC patients with SACE level II or III (substasis) during TACE over those with SACE level IV (total stasis) [25.6 (95% CI 16.2–35.0) vs. 17.1 (95% CI 13.3–20.9) months, $p = 0.035$]. In addition, they stated that SACE level IV was independent of baseline characteristics including Child–Pugh class as a negative predictor for OS [HR 2.49 (95% CI 1.41–4.42), $p = 0.002$] suggesting that moderate embolization leading to substasis is more favorable than overembolization ending in stasis [22]. In contrast, the present study could not confirm any direct influence of SACE level on PFS or OS (Kaplan–Meier analysis: log rank test: $p = 0.83$ and 0.55, respectively, Cox regression for OS: $p > 0.5$). SACE might have an indirect impact on OS as SACE showed a significant positive correlation with mRECIST tumor response and mRECIST significantly predicted OS. Moreover, SACE had a confounding aspect in mRECIST classification independently predicting OS. As the higher the SACE score, the higher the tumor response (mRECIST), the consequence for the interventionist could be to strive for the highest embolization as possible during DEB-TACE. Kwan et al. showed that subjective absence of residual contrast enhancement correlated with histopathological near-complete necrosis (> 90%) favoring the prior statement [17]. To avoid ischemia of healthy liver tissue risking poorer outcome for the patient, the catheter should be placed super selectively in the tumor feeding artery during DEB-TACE. Following these controversial results, the correct angiographic endpoint is yet to be discovered and needs prospective studies with higher patient number.

Our study had some limitations. First, the study was a single-center retrospective analysis with a moderate patient number. Second, time of control CT was not the same among all patients possibly leading to differences in CT measurement results. Third, SACE is a subjective rating that might lead to variable results as it is operator dependent. Objective quantitative angiographic endpoints correlating with survival should be developed and analyzed. Fourth, the tumor burden could have influenced the level of selectivity during DEB-TACE. Fifth, the exact way we calculated density measurements have to our knowledge only partly been published before (Choi et al. [18]). Thus, to compare our results about tumor density change with other scientific studies is not thoroughly possible. Sixth, the use of Lipiodol in some sessions could have had an influence on density results. Seventh, in the OS and PFS analysis the aspect of additional therapy was apart from censoring at operation or radiofrequency ablation not taken into account, which could have influenced the results in a positive way. Eighth, as an indirect impact of SACE on OS and PFS rather than a direct correlation was shown, the relevance of these results for the interventionist should be validated in further studies.

Conclusion

A direct impact of SACE on PFS or OS after DEB-TACE in patients with HCC could not be shown. However, SACE significantly correlated with local and overall mRECIST tumor response that again significantly predicted OS. We therefore postulate an indirect impact of SACE on OS, consequently complete embolization should be attempted.

Acknowledgements The authors would like to thank PD Dr. Med. Bruno Neuner, Campus Virchow-Hospital, Charité Berlin, as well as Sebastian Häckl and Florian Lasch, Institute for Biometry, Hannover Medical School for their statistical guidance throughout the study.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This study was reviewed and approved by the Ethical Committee of Hannover Medical School, Germany.

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